REMARKS:

The Examiner's Office Action has been reviewed and considered, and revised claims are submitted in light of the Examiner's comments.

The Examiner in his first communication of 01.06.2003 suggested dividing the application in five different subjects or five different compositions and methods for lowering serum cholesterol in human subjects. The compositions should have comprised a single higher primary aliphatic alcohol or the alcohol and one or more components selected from a group of sterols or sterol esters. The alcohols in question were octadecanol, eicosanol, docosanol, tetracosanol and hexacosanol.

To summarize briefly, the application in reference discloses the utilization of a novel mixture of higher primary aliphatic alcohols isolated from tall oil (wood alcohols) for the manufacture of food and pharmaceutical formulations for the reduction of serum cholesterol levels. Several examples of food and pharmaceutical formulations and their preparation are provided, and evidence for the serum cholesterol lowering effect of the mixture of alcohols is provided (see Example 12, 13).

Also, evidence for the synergistic effect of serum cholesterol lowering of formulations containing wood alcohols and **esterifyed** wood sterols (sterols isolated from tall oil) is provided.

The newly amended claims are carefully drawn to subject-matter that is disclosed in the specification. As it is evident from the application as filed, the novelty and inventiveness of the invention relates at least in part to the use of alcohols for the manufacture of food products or medicaments for the reduction of serum cholesterol levels. Therefore independent claims have been drawn to theses subjects. No distinction is made of compositions of wood alcohols, because these alcohols are not characterised by the process used for their isolation from tall oil, but they are characterized by a unique composition of alcohols. Using different processes for their isolation do not alter their uniqueness, only their relative proportion in the mixture. In addition the application discloses that "the term wood alcohols stands for a mixture of

octadecanol, eicosanol, docosanol, tetracosanol, and hexacosanol" and Tables I, III and IV provides examples of such mixtures.

Formulations further containing esteryfied wood sterols are claimed dependently, although, the synergistic effect of higher primary aliphatic alcohols together with (esterifyed) sterols is neither obvious nor known in the art.

Non-obviousness

Claim 1 is not addressed to an invention of selection but to a novel, alternative solution to the problem of lowering serum cholesterol levels. Therefore the question to answer is not whether the disclosed composition has or does not have any surprising technical effect, but whether the use of these compositions in food and pharmaceutical formulations for the manufacture of food products or medicaments for the reduction of serum cholesterol levels would have been obvious to the person skilled in the art, having regard the state of art at the time the invention was made.

In addressing the question of non-obviousness we have to determine the scope and content of the prior art, then to look into the differences between the prior art and the new claims. Then to resolve the level of the person skilled in the art, and in view of the above, to try to figure out if the invention would have been obvious to such a person.

The Cited Art

According to the Examiner, the closest prior art is US 5,952,393 ("Sorkin"). In describing the state of art, Sorkin notes that the term policosanol comprise a mixture of high molecular weight aliphatic alcohols, isolated from a number of different plant sources, and that the major components in said mixtures are octacosanol (C28) and triacontanol (C30). In fact the content of these alcohols in sugarcane wax and rice bran wax, which were known at the time of Sorkin's invention, can be as high as 85% and 70% respectively. Most of the studies over the serum cholesterol lowering effect of policosanols quoted by the inventor, were made using policosanol from rice bran wax. As far as the effect of individual alcohols concerns, only octacosanol (Kat, S et.al, quoted in "other references" in Sorkin) and hexacosanol (JP-A-62099323) have been investigated and shown to have cholesterol lowering effect. Later

disclosure (US 6,225,354) teaches the cholesterol lowering effect of policosanol from beeswax, whose total content between octacosanol and triacontanol can reach up to 86 %.

In the Table I below the compositions of policosanol from sugarcane wax, rice bran wax, beeswax and from tall oil of the present application are shown. (The relative composition of alcohols in rice bran wax policosanol was obtained from data of Table 1 of Sorkin, taking into account that the total alcohol content of the "Rice Bran Wax" is 23-33%)

Table I: Range of compositions in weight % of policosanols from different sources.

	Plant wax alcohols			**Wood alcohols from tall oil**
ALYPHATIC ALCOHOLS Name and number of carbon atoms in molecule	**SUGARCANE WAX US Patent N° 5,856,316**	**RICE BRAN WAX US Patent N° 5,952,393**	**BEESWAX US PatentN° 6,225,354**	**Application 01 306 414.2-1221**
Octadecanol (18)	0	0	0	0.001 –10.0
Eicosanol (20)	0	0	0	1.0 – 25.0
Docosanol (22)	0	1 – 1.6	0	10.0 – 60.0
Tetracosanol (24)	0.5 - 1	9.7 – 14	1 - 4	20.0 – 60.0
Hexacosanol (26)	5.5 – 8.5	8.9 – 12.7	7 - 12	1.0 – 30.0
Heptacosanol (27)	2- 3.5	0	1- 4	0
Octacosanol (28)	60- 70	16.9 – 24.3	30 – 60	0
Nonacosanol (29)	0.4 –1.2	0	2 – 5	0
Triacontanol (30)	10 – 15	25.3 – 36.3	16 – 26	0
Dotriacontanol (32)	4 – 6	14.1 – 20.2	13 – 22	0
Tetratriacontanol (34)	0.4 – 2	6.7 – 9.6	2 – 6	0
Hexatriacontanol (36)	0	1.5 - 2.2	0	0

US Patent 5,856,316 claims only the use of said policosanol as antiplatelet, anti-ischemic and antithrombotic agent, the cholesterol lowering effect of the disclosed mixture have been previously shown by one of the inventors (Arruzabala) quoted in Sorkin, and published in different papers. US Patent 6,225,354 discloses the use of policosanol from beeswax as cholesterol lowering agent and shows examples teaching said effect.

By contrast, in Sorkin there is only a presumption as to the cholesterol lowering effect of rice bran policosanol, but no examples are provided as evidence to this effect. Presumably, given the close resemblance of sugarcane wax policosanol and rice bran wax policosanol compositions,

the inventor took it for granted that the latter would be also effective for the lowering of serum cholesterol. This is, at best, a questionable theory, raising questions on industrial applicability. Still, to the person of skill it would have been hard to find obvious that the commercial preparations utilized in the examples of Sorkin, that is the product under the brand name of "Rice Bran Wax" containing only from 23 to 33 % of policosanol (see Table I of Sorkin), without any knowledge as to the nature of the other major constituents of "Rice Bran Wax", had similar cholesterol lowering effect as that of sugarcane wax policosanol. Sorkin is questionable as a basis for an obviousness rejection of claims to the use of the composition for the manufacture of food product or medicament for the reduction of serum cholesterol levels. There is very little, if any, teaching in Sorkin regarding such uses for the compositions discloses therein.

Table II below summarizes the differences between compositions of the state of art and "wood alcohol."

Table II. Summary of main qualitative and quantitative differences between compositions of Table I

Alcohols	Sugarcane wax US 5,856,316	Rice Bran Wax US 5,952,393	Beeswax US 6,225,354	Wood alcohols from tall oil
C18 - C26	6 -9.5	10.7- 15.6	8 – 16	100
C28 – C36	90.5 - 96	84.4 – 89.4	84 – 98	0
Octacosanol (C28)	60 - 70	16.9 – 24.3	30 – 60	0
Triacontanol (30)	10 -15	25.3 – 36.3	16 – 26	0

Figures in Table II shows that "wood alcohol" is a unique mixture of alcohols, characterized by a narrow distribution of chain lengths from C18 to C26, though its main components are docosanol and tetracosanol, essentially absent from the other mixtures. All other known plant alcohols have wide chain length distribution form C24 to C36, and in all of them the first major component is octacosanol and the second major component is triacontanol, neither of them found in wood alcohol. The three mixtures of state of art are composed of mainly by alcohols from C28 – C36.

(a) **The Skilled Person**

The pertinent art of the invention is related to human health and nutrition, therefore the skilled person knows about the health adverse effects of high serum cholesterol levels and is also aware of the current dietary or pharmacological approaches to reduce said levels. Dietary measures the person of skill is aware of, include daily intake of certain amounts of phytosterols or certain long chain fatty alcohol or mixtures of long chain fatty alcohols. The person of skill is aware as well of the mechanism of action of the phytosterols in reducing serum cholesterol levels. The biochemical basis for the action of phytosterols have been elucidated, and it is related to their structural similarity to cholesterol. With respect to the effect of long chain aliphatic alcohols on serum cholesterol levels, the current state of empirical knowledge can be summarized as follows:

- Hexacosanol (C26) and octacosanol (C28) each one separately, are effective;
- Sugarcane wax alcohol and beeswax alcohol mixtures are effective; the major alcohol component in both mixtures is octacosanol
- The person of skill is also aware of the fact, that rice bran wax alcohols have not been shown effective, but instead they were supposed to be so. Octacosanol is also the major alcohol component in this mixture.

The skilled person is aware as well, that in the case of long chain alcohols, "their mechanism of action of action has not yet been elucidated". This fact leave several important questions unanswered, like the following:

- Are each naturally ocurring long chain alcohols from C18 to C36, besides of C26 or C28, also effective for reducing serum cholesterol levels?
- If they were, are they equally effective or there is chain length dependency?
- Are there some alcohols which are not effective at all?
- Are there some alcohols having the opposite effect?
- Is there synergism in mixtures of alcohols of differing chain lengths?

It the absence of a comprehensive mechanism of action of the relation of the long chain alcohols to account for their cholesterol lowering capacity together with the lack of a sufficiently

large body of empirical knowledge in the subject, none of the above questions can be answered today.

Therefore it would and could not have been obvious to the person skilled in the art, having regard to the state of art, that the composition of wood alcohols were also effective for the reduction of serum cholesterol levels. Having regard the state of art, the skilled person would not have been motivated at all for selecting a mixture of alcohols lacking almost all of the components in the state of art, to be used for reduction of serum cholesterol.

(b) **Synergistic Effect Of Wood Alcohols And Wood Sterols**

Sorkin provides a mixture of rice bran wax policosanol (which we emphasize is only presumptively cholesterol lowering) with phytosterols which together "are to be expected to have a synergistic effect." No examples are provided to back this affirmation. Therefore, either it is obvious to combine both kind of compounds or it is not. If it were the first, then the invention, as far as use is concerned would be obvious and non patentable over the prior art.

But, synergistic effects are rarely obvious. The synergism of the present invention is not shown, disclosed or enabled by Sorkin, which is at best a vague intimation of a general idea which may or may not be workable.

It is Applicant's belief that this application is in a condition for allowance. An action so indicating is respectfully requested. If the Examiner believes that discussion of this application would be beneficial, the undersigned may be contacted at the telephone numbers indicated below.

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Respectfully submitted,

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